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Heparin and Enoxaparin in Infants and Children: Literature Update

Marcia L. Buck, Pharm.D., FCCP, FPPAG

Anticoagulation remains one of the most complicated therapeutic areas within pediatric pharmacology. Developmentally-related changes in the pharmacokinetic and pharmacodynamic characteristics of these agents, in combination with physiologic changes in coagulation during growth, produce significant challenges to optimizing both dosing and monitoring. Several recently published studies of heparin and enoxaparin have added to our understanding of anticoagulation in the pediatric population. This issue of *Pediatric Pharmacotherapy* will describe these papers as well as recent reviews and some thought-provoking studies conducted in adults that may shape our monitoring of anticoagulation in the future.

Pediatric Anticoagulation Review

For readers new to this area or needing a quick refresher, a concise topic review was published earlier this year in *Thrombosis Research*.[1] In just five pages, the author covers traditional therapy with heparins and vitamin K antagonists and provides insight into the newer agents not yet routinely used in children. The article contains several interesting tables, including one comparing the dates of discovery, first use in adults, first use in children, and publication of the first pediatric prospective study for all of the anticoagulants currently in use. The difficulties in performing pediatric studies are clearly reflected in the time lag between the introduction of heparin and warfarin (1934 and 1954, respectively) and the first prospective clinical trials documenting their efficacy and safety in 1994.

Use of Treatment Guidelines

Pediatric health care providers working with patients requiring anticoagulation should have access to the most recent consensus guidelines on antithrombotic therapy in children, which were published by the American College of Chest Physicians in *Chest*.[2] These evidence-based clinical practice guidelines serve as the foundation for patient care, but are also limited by the relative lack of research in the pediatric population.

Earlier this year, Peng and colleagues at the University of Melbourne Royal Children's Hospital, a group which included one of the authors of the *Chest* guidelines, examined compliance with the guidelines in children at their institution.[3] A total of 526 hospitalized children received an antithrombotic during the 100-day observation period, resulting in 5,885 episodes of drug administration. Complete adherence to the guidelines, including both indication and drug dosing, was demonstrated in only 49.5% of the treatment courses. The greatest area of disagreement between clinical practice and the guidelines was in the routine use of heparin to maintain patency of central venous lines, which is not currently a recommendation. The authors suggest that the relatively low level of compliance with the guidelines at their institution may result from a lack of confidence in the strength of evidence supporting the recommendations. Areas highlighted for future research included the use of heparin for central lines as noted previously, as well as the routine use of heparin flush solutions and the need for prophylaxis in infants and children with veno-occlusive disease or during periods of immobility.

Enoxaparin Dosing Requirements

Two recent papers have confirmed earlier work demonstrating the need for higher enoxaparin doses in infants and young children.[4,5] In another study conducted at the University of Melbourne Royal Children's Hospital, Ignjatovic and colleagues reviewed the records of 233 patients (ages 3 days to 16 years) treated with enoxaparin between October 2003 and July 2007.[4] Of those patients, 140 had at least one anti-Factor Xa (anti-Xa) assay performed during treatment and were included in the analysis. All

patients received enoxaparin 0.5-0.75 mg/kg twice daily. The majority of patients (81%) were being treated with enoxaparin for a diagnosed clot, with the remaining 19% receiving enoxaparin as prophylaxis. Use of anti-Xa monitoring was more frequent in patients under a year of age compared to older children and in patients treated for more than 60 days compared to those with shorter treatment courses (both comparisons, $p < 0.05$). Only 55 patients (39%) had an anti-Xa value within the target range of 0.5-1.0 IU/mL. Seventy-three patients (52%) were subtherapeutic and 12 (9%) had values above 1.0 IU/mL. More infants than older children were subtherapeutic on their initial enoxaparin regimen ($p < 0.05$).

The average enoxaparin dose required to achieve a therapeutic anti-Xa in patients being treated for a clot was significantly higher in the younger age groups than in the two older groups, with a mean dose of 1.59 ± 0.47 mg/kg in the patients < 2 months, 1.48 ± 0.47 mg/kg for those 2 months-1 year, and 1.19 ± 0.22 mg/kg in those 1-5 years, compared to 0.98 ± 0.18 mg/kg in children 6-10 years and 0.98 ± 0.13 mg/kg in the 11-16 year old children ($p < 0.05$). While age played a significant role in enoxaparin dose response, the authors observed that there was no difference in dosing requirements between infants born prematurely and those born at term. Forty-one patients (29%) experienced minor bleeding, but only one case of major bleeding occurred. In the 73 patients for whom an outcome was recorded, 17 (23%) had complete clot resolution, 36 (49%) had partial resolution, 15 (21%) had no change and 5 (7%) had clot extension. As in previous studies, the authors concluded that current dosing recommendations are not adequate for patients up to 5 years of age.

Sanchez de Toledo and colleagues found a similar need for higher enoxaparin doses in infants and young children in their cardiac intensive care unit.[5] Thirty-one patients were included in the retrospective study, ranging in age from birth to 2 years; 25 (81%) had recently undergone cardiac surgery. Twenty-one patients (68%) were receiving treatment doses and the remainder were receiving prophylaxis. For analysis, the patients were divided into two groups: younger patients (0-2 months of age) and older patients.

Both age groups required an increase in their enoxaparin doses to achieve an anti-Xa value within the target range. In the younger patients, the mean enoxaparin dose increased from 1 mg/kg to 1.87 mg/kg in those receiving prophylaxis and from 1.5 mg/kg to 2.37 mg/kg in those receiving treatment (therapeutic) doses ($p < 0.02$ for both). In the older patients, the dose increase in the prophylaxis group, from 0.73 mg/kg to 1.06 mg/kg was not statistically significant. There was a significant increase, however, in the treatment doses, from 1.23 mg/kg to 1.82 mg/kg ($p = 0.002$). The average number of dosage adjustments required to achieve an appropriate anti-Xa value was similar in the two age groups: 2.8 ± 1.2 in the younger patients and 1.9 ± 1.7 in the older patients. No difference in dosing requirements was found between those patients who received direct subcutaneous injection and those using an Insuflon® device. No bleeding complications were identified.

A third study, published last year in the *Journal of Thrombosis and Haemostasis*, provides an interesting variation on traditional enoxaparin dosing.[6] Using anti-Xa values and dosing information collected from 126 children and young adults (newborn-25 years of age, median 5.9 years), Trame and colleagues developed a population pharmacokinetic model that would allow prediction of anti-Xa activity resulting from both 12- and 24-hour dosing schemes. Their focus was to explore the feasibility of once daily enoxaparin for prophylaxis. Using the model developed, 53% of patients receiving once daily dosing would achieve the anti-Xa goals of 0.3-0.8 IU/mL at 4-6 hours post-dose and 0.1 IU/mL at the end of the dosing interval. Based on their results, the authors propose that once daily dosing may be feasible for some children requiring enoxaparin prophylaxis, provided that anti-Xa monitoring is conducted to ensure adequate anticoagulation.

Appropriate Dosing for Obese Children

The concern for suboptimal anticoagulation in obese adults receiving heparin has led to questions about the efficacy of traditional weight-based heparin dosing in children. In the July issue of *Annals of Pharmacotherapy*, Moffett and colleagues reported the results of their retrospective study of the effects of weight on heparin use in children undergoing cardiac catheterization.[7] The authors compared 39 children between 2 and 18 years of age with a body mass index (BMI) greater than the 95th percentile for age with 39 non-obese controls. The obese patients had an average BMI of 25.8 ± 5.8 kg/m^2, while the average BMI of the controls was 18.2 ± 2.9 kg/m^2. All patients received a single heparin dose of 50-100 units/kg, with subsequent doses given if the activating clotting time (ACT), measured at 1 hour intervals during the procedure, was less than 250 sec.

The authors found no significant difference in the mean total dose of heparin administered during cardiac catheterization, with an average dose of 72.3 ± 24.9 units/kg in the obese children and

63.6 ± 23.6 units/kg in the controls (p = 0.12). There was also no difference in the 1 hour post-heparin ACT, with a mean of 315.7 ± 118.9 sec in the obese patients and 358.3 ± 114.9 sec in the controls (p = 0.11) or in the percent change in ACT after total heparin administration (196% in the obese children compared to 165% in the controls, p = 0.17). Although the authors found little evidence of a difference in heparin requirements in obese children, they suggest that further studies are needed to confirm or refute these findings.

In contrast, Lewis and colleagues reported the need for increased enoxaparin doses in a series of three obese children receiving venous thromboembolism (VTE) prophylaxis.[8] The patients, an 81.5 kg 11-year-old and two 16-year-olds weighing 294 and 358.6 kg, were initially treated with a standard enoxaparin prophylaxis dose of 40 mg given once daily. At this dose, all three had subtherapeutic anti-Xa values (< 0.15 IU/mL). Two patients were increased to an enoxaparin dose of 40-45 mg twice daily, while the dose in the largest patient was eventually titrated up to 100 mg every 12 hours, achieving an anti-Xa value of 0.29 IU/mL. In spite of continued low anti-Xa values, all of the patients remained on therapy and none developed VTE. While representing only three patients, these results are in agreement with previous studies in adults suggesting an increased enoxaparin clearance in obese patients and the need for higher doses. Larger prospective studies of both heparin and enoxaparin are needed to better guide dose selection and titration in obese children.

Efficacy of Low-dose Heparin Infusions

Several pediatric cardiac programs have incorporated the use of low-dose heparin infusions (typically 10 units/kg/hr) in the post-operative setting to prevent thrombus formation in central venous catheters or intracardiac catheters. The efficacy of this practice has not been well studied. Last year, Schroeder and colleagues conducted the first randomized, double-blind, placebo-controlled study of low-dose heparin in infants following cardiac surgery.[9] The patients were randomized to receive either heparin 10 units/kg/hr or placebo (5% dextrose). The time of initiation was determined by the clinical team. A total of 101 infants were enrolled, with 90 completing the study. The treatment and placebo groups were similar in age, weight, and the surgeries performed. The mean cardiopulmonary bypass time was longer in the heparin group (160 min versus 83 min in the controls), but the difference did not reach statistical significance.

The rates of thrombosis or catheter malfunction were not significantly different between the groups. Eight of the 53 infants in the heparin group (15%) had a documented clot compared to 6 of the 37 controls (16%, p = 0.89). Multivariate analysis revealed that use of a catheter for 7 days or more was associated with a greater risk for thrombosis (odds ratio 4.3, p = 0.02). In contrast, study group assignment (i.e. the use of low-dose heparin), single-ventricle anatomy, and age < 30 days were not associated with an increased risk. Of note, the authors observed that use of multiple catheters in the same patient did not appear to increase the risk of clot formation. There was also no difference in the incidence of catheter-associated bloodstream infections between the groups, with four documented in the heparin group and three in the controls (p = 0.78).

While low-dose heparin is not typically expected to produce a significant elevation in aPTT, there was a significant difference in mean aPTT values between the groups (52 sec versus 42 sec in the controls, p = 0.001). The difference was most pronounced in the patients < 30 days of age, with a mean aPTT of 63 sec in the heparin group and 43 sec in the controls, p = 0.008). The authors concluded that while low-dose heparin was safe in this patient population, it did not appear to decrease the incidence of catheter-related thrombosis or catheter malfunction.

Monitoring

Anti-Xa monitoring has become a widely accepted tool for optimizing enoxaparin dosing in infants and young children. A growing number of studies suggest that anti-Xa may be a more appropriate tool for assessing heparin therapy than the traditional activated partial thromboplastin time (aPTT). While aPTT testing has the advantages of its greater availability, ease of use, and cost, increasing concern over variation in reagents and variability due to extraneous factors have led clinicians to look to the anti-Xa assay as a more predictable test.

A recent paper conducted in adults may shed light on the utility of the anti-Xa assay in children. In an observational study of 100 adults, Guervil and colleagues assigned 50 patients receiving heparin to each testing method.[10] All patients were given a standard 80 units/kg heparin bolus dose followed by an infusion of 18 units/kg/hr. Subsequent dosing rate changes were made per protocol, based on target anti-Xa or aPTT values. The mean time to achieve a therapeutic monitoring test was significantly less in the anti-Xa group (28 ± 16 hours compared to 46 ± 26 hours in the aPTT group, p < 0.001). At both 24 and 48 hours, there were greater percentages of patients with therapeutic

anticoagulation (values within the target range) in the anti-Xa group. Patients in the anti-Xa group also had significantly fewer tests performed per day ($p < 0.0001$) and fewer heparin infusion rate changes per day ($p < 0.01$). The results of this study, that anti-Xa monitoring may provide a better option for heparin monitoring than the traditional aPTT, confirm those from several earlier papers.

While the utility of anti-Xa monitoring for heparin has been demonstrated in the clinical setting, the actual correlation between monitoring techniques remains unclear. In 2010, Newall and colleagues published a study comparing aPTT and anti-Xa testing to protamine titration and thrombin clotting time (TCT) in children.[11] The authors monitored 55 children (ages 6 months to 15 years) receiving heparin during cardiac catheterization at a single center over a 2 year period. All patients had baseline coagulation studies prior to and following a single IV heparin dose of 75-100 units/kg (mean dose 96.2 $\pm$ 1.1 units/kg).

Overall, correlation between the two routine monitoring tests and either protamine titration or TCT was poor, with a correlation coefficient ranging from 0.11 to 0.68. Only 25% of the anti-Xa values were within the target range of 0.35-0.7 IU/mL. Of those samples, 72% had supratherapeutic results by protamine titration (values greater than 0.4 IU/mL). The aPTT values correlated with this group of samples ranged from 97 to 287 sec, with a mean of 217 $\pm$ 114 sec, considerably above the aPTT target range. Based on their data, the authors concluded that the currently used assay techniques are not equivalent and suggest that current monitoring recommendations are not adequate for optimal heparin dosing in children.

Summary

Anticoagulation remains a therapeutic challenge in the pediatric population. Several studies have been published within the past two years which have provided us with valuable new information on the dosing and monitoring of heparin and enoxaparin in infants and children. Additional studies are needed, however, to provide confirmation of these findings and to determine the optimal use of these agents, as well as newer anticoagulants, in pediatric practice.

References

1. Young G. New anticoagulants in children: a review of recent studies and a look to the future. Thrombosis Res 2011;127:70-4.
2. Monagle P, Chalmers E, Chan A, et al. Antithrombotic therapy in neonates and children: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). Chest 2008;133:887-968.
3. Peng C, Doan J, Monagle P, et al. Compliance of antithrombotic management at a tertiary pediatric hospital with international guidelines: a 100-day audit. Thrombosis Research 2011;128:135-40.
4. Ignjatovic V, Najid S, Newall F, et al. Dosing and monitoring of enoxaparin (low molecular weight heparin) therapy in children. Br J Haematol 2010;149:734-8.
5. Sanchez de Toledo J, Gunawardena S, Munoz R, et al. Do neonates, infants and young children need a higher dose of enoxaparin in the cardiac intensive care unit? Cardiol Young 2010;20:138-43.
6. Trame MN, Mitchell L, Krümel A, et al. Population pharmacokinetics of enoxaparin in infants, children and adolescents during secondary thromboembolic prophylaxis: a cohort study. J Thromb Haemost 2010;8:1950-8.
7. Moffett BS, Teruya J, Petit C. Heparin dosing in obese pediatric patients in the cardiac catheterization laboratory. Ann Pharmacother 2011;45:876-80.
8. Lewis TV, Johnson PN, Nebbia AM, et al. Increased enoxaparin dosing is required for obese children. Pediatrics 2011;127:e787-e790.
9. Schroeder AR, Axelrod DM, Silverman NH, et al. A continuous heparin infusion does not prevent catheter-related thrombosis in infants after cardiac surgery. Pediatr Crit Care Med 2010;11:489-95.
10. Guervil DJ, Rosenberg AF, Winterstein AG, et al. Activated partial thromboplastin time versus antifactor Xa heparin assay in monitoring unfractionated heparin by continuous intravenous infusion. Ann Pharmacother 2011;45:861-8.
11. Newall F, Ignjatovic V, Johnston L, et al. Clinical use of unfractionated heparin in children: time for change? Br J Haematol 2010;150:674-8.

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee at their August meeting:

1. The capsaicin 8% patch (Qutenza®) was added to the Formulary for outpatient use.

2. Factor IX Complex (Profilnine®) was added with restriction to use based on the Reversal of Oral Anticoagulation – Factor IX clinical practice guideline.

3. Gadobutrol (Gadvist™) a gadolinium-based contrast agent was rejected due to lack of evidence of superiority over currently available agents.

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